Importance of Antigenic Composition of Influenza Virus Vaccine in Protecting against the Natural Disease*†

Observations during the Winter of 1947–1948

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AS is now well known, convincing evidence was gathered in 1943–1944,[1–3] and again in 1945–1946 [4, 5] indicating that susceptibility to epidemic influenza could be modified by subcutaneous vaccination. The procedure found to be effective on those two occasions was repeated again in the winter of 1946–1947.[6] This time, however, it was without demonstrable effect.

The failure of vaccination to influence susceptibility in the spring of 1947 was readily explained by the finding that the virus then in circulation was significantly different antigenically from the virus-antigens included in the vaccine.[6–11] It is of special interest, too, that the 1947 virus, although similar to a strain isolated in Australia in the fall of 1946,[12] differed from others that had been isolated in previous outbreaks.

These experiences emphasized the desirability of continuing the field studies of vaccination against influenza for evaluation in future epidemics. The matter was discussed at a meeting of a committee of the Army Epidemiological Board and of representatives of the Office of the Surgeon General of the Army. The members of the committee were Dr. Colin M. MacLeod, Dr. Thomas Francis, Jr., Dr. John H. Dingle, Dr. Joseph E. Smadel, and Dr. Jonas E. Salk. The representatives of the Office of the Surgeon General were Col. Tom F. Whayne, Lt. Col. Frank L. Bauer, and Lt. Col. Arthur Long. At this meeting, plans were inaugurated for carrying out field studies in the Army, under the auspices of the Commission on Influenza. The observations reported here comprise the results of the first year's effort in a program that will be continued over a number of years, and until the required information is obtained.

PLAN OF THE STUDY

It is desired to explain the limiting circumstances that prevailed at the time of planning the 1947–1948 study. Before this particular investigation was contemplated the policy of the Army had already been adopted to vaccinate

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all troops in the fall or early winter of that year. A new supply of vaccine was ordered and it was to contain the strain of virus that had by-passed the vaccine used in the preceding winter and spring. Because the quantity of new-formula material that could be promised for delivery in the fall was insufficient to supply the entire Army, it had been decided to supplement this limited amount with old-formula material to be used in certain specified areas.

Under the circumstances then prevailing the inclusion of an *unvaccinated* control group could not be considered in any trials that were to be carried out in the Army. The only kind of a study that could be conducted was one in which a comparison would be made between groups given the *two different* vaccines. The two vaccine preparations were the same in so far as both contained the Type A and Type B components, but they differed in respect to the presence or absence of the new component that is now referred to as Type A-prime.

It is obvious that a study of this sort would yield information on the efficacy of vaccination only if the virus operating during the period in question were similar to the one present in the new vaccine and absent from the other. Although this plan was far from ideal, it did serve the purpose of initiating the field trials in the Army without further delay and offered the opportunity to gain experience that would be of value the following year.

PROCEDURE

Accordingly, arrangements were made for a study to be conducted at Fort Dix, New Jersey. Approximately 60 per cent of the strength of this induction and training center of 15,000 were trainees who remained for approximately 13 weeks; the remainder were cadre and personnel of the post detachments.

The scheme for distributing the two vaccines equally in the population was to give the *old-formula* material to men with serial numbers ending in *odd* digits and the *new material* to men with numbers ending in *even* digits. On November 14, 1947, all of the trainees and cadre of the training companies were inoculated according to this scheme, and in the following week the detachments were similarly treated. Subsequently, the same plan was employed in the treatment of all newly formed companies. Influenza vaccine was administered along with the other immunizations at the time of medical processing, thereby maintaining the division of the entire post into two groups. Great care was exercised to maintain the distribution of the vaccines according to the serial-number scheme and to reduce exceptions and error to a minimum. This procedure was continued until April 1, 1948.

The two vaccines used in this study were prepared commercially. The *old-formula material* was from a single batch of vaccine prepared for use in the winter of 1945–1946.[4] The virus in this vaccine was concentrated by the method of red cell adsorption-elution.[13] At the time of use in this study the vaccine was more than two years old; and this was about one year beyond the expiration date. The strains of virus in this vaccine were PR8 and Weiss, Type A, and Lee, Type B. The *new-formula material* was from a single batch, freshly prepared just a few months prior to use in this study. Concentration of virus was affected by Sharples centrifugation,[14, 15] and the strains represented were PR8 (Type A), FM1 (Type A-prime) and Lee (Type B).

Even though the two vaccines differed in strain composition it was still necessary to evaluate serologically the effect of each in terms of their different antigenic components. This was done by comparing antibody titers in serum collected before and again two weeks

TABLE 1

Geometric Mean Antibody Titers Before and Two Weeks After Vaccination in Subjects Inoculated with "Old-Formula" and "New-Formula" Influenza Virus Vaccine*

Antigen in Serological Test	"Old-Formula" Vaccine (142 Subjects)			"New-Formula" Vaccine (81 Subjects)		
	Pre-Vacc.	Post-Vacc.	-Fold Change	Pre-Vacc.	Post-Vacc.	-Fold Change
PR8	70	536	7.7	65	440	6.8
LEE	80	880	11.0	75	640	8.5
FM1	68	163	2.4	73	438	6.0

"Old-Formula Vaccine" was from the supply prepared for use in the winter of 1945–1946 and had an expiration date of December, 1946. It was administered to these subjects on November 14, 1947. This vaccine contained the PR8 and Weiss Strains of Type A and the Lee Strain of Type B virus.

"New-Formula Vaccine" was freshly prepared just a few months prior to use in November, 1947. It contained the PR8 and FM1 strains of Type A and the Lee strain of Type B virus.

* Antibody titers (agglutination-inhibition) are expressed in terms of the dilution of serum inhibiting 4 units of hemagglutinin.

after inoculation. The data, for groups of individuals given the different vaccines, are summarized in Table 1 in terms of the geometric mean titer as well as the -fold increase as measured with three different antigens. Although the *old-formula vaccine* induced a distinct elevation in antibody level for the PR8 and Lee antigens, there was only a slight increase in antibody for the FM1 antigen. The *new vaccine* was distinctly more effective than the *old* in terms of the antibody response measured with the FM1 antigen. It is interesting to note that the older preparation, although one year beyond its expiration date, appears to have induced a somewhat better response than the new material to the PR8 and Lee components.

The antigenicity of the two vaccines was also tested in mice and they were found to be equally effective with respect to the PR8 (Type A) and Lee (Type B) components. As was to be expected the *old-formula vaccine* failed to induce the formation of any antibody for the FM1 strain (Type A-prime), while the new material was as effective in the formation of antibody for FM1 as it was for the PR8 and Lee strains.

OBSERVATIONS

In planning the clinical and epidemiological aspects of the study it had been decided to base any evaluation of vaccination effect upon the number of cases of respiratory disease hospitalized or put on quarters. Although the limitation of this procedure is thoroughly appreciated it was believed to be sufficiently reliable to evaluate the crude data obtained in this manner, particularly since the groups were to be equal in size and were to be treated in the same way. Moreover, an adequate sampling of cases for serological study was to be made.

After the study was begun careful records were kept of all admissions to hospital or to quarters for reasons of respiratory disease. In addition, records were kept of the number of admissions to hospital from the odd and even serial-numbered groups for other illnesses as well.

Before presenting the data it is desired to point out that proven cases of influenza among patients in Army hospitals have usually been found among those diagnosed as "nasopharyngitis," or occasionally as "laryngitis" or "bronchitis." Even though the systemic component of the illness may predominate and may strongly suggest the diagnosis of Influenza, this diagnosis is not used and preference is given to the terms referring to the area of the

TABLE 2

Tabulation of Number of Cases of Nasopharyngitis, Laryngitis, and Bronchitis that Occurred Each Week in "Odd" and "Even" Groups Given "Old-Formula" and "New-Formula" Vaccine, Respectively. Fort Dix, New Jersey, 1947–1948

			Number of Cases *		Cumulative Total		Difference
Month	W/E	Mean Strength	Odd	Even	Odd	Even	Odd-Even
December	5	13,226	7	5	7	5	+ 2
	12	12,517	14	20	21	25	— 4
	19	12,422	16	8	37	33	+ 4
	26	12,448	2	0	39	33	+ 6
January	2	11,900	2	9	41	42	— 1
	9	12,192	15	9	56	51	+ 5
	16	12,916	15	16	71	67	+ 4
	23	13,740	40	34	111	101	+10
	30	14,077	48	38	159	139	+20
February	6	14,199	84	65	243	204	+39
	13	14,375	77	63	320	267	+53
	20	14,566	61	49	381	316	+65
	27	14,907	49	47	430	363	+67
March	5	15,108	44	56	474	419	+55
	12	15,541	47	33	521	452	+69
	19	15,639	58	64	579	516	+63
	26	16,216	26	34	605	550	+55
April	2	16,261	39	20	644	570	+74
	9	16,895	10	20	654	590	+64
	16	17,017	17	15	671	605	+66
	23	16,832	18	15	689	620	+69
	30	16,681	32	37	721	657	+64
May	7	16,463	39	24	760	681	+79
	14	15,748	33	23	793	704	+89
	21	15,297	19	21	812	725	+87
	28	13,905	33	25	845	750	+95
June	4	14,016	15	10	860	760	+100
	11	14,131	18	11	878	771	+107
	18	14,152	11	14	889	785	+104
	25	14,579	18	19	907	804	+103
July	2	14,856	16	18	923	822	+101

* Hospitalized or put on quarters

FIGURE 1

Comparison of Weekly Incidence of Nasopharyngitis, Laryngitis and Bronchitis in Two Groups Given Old-formula and New-formula Influenza Virus Vaccine.

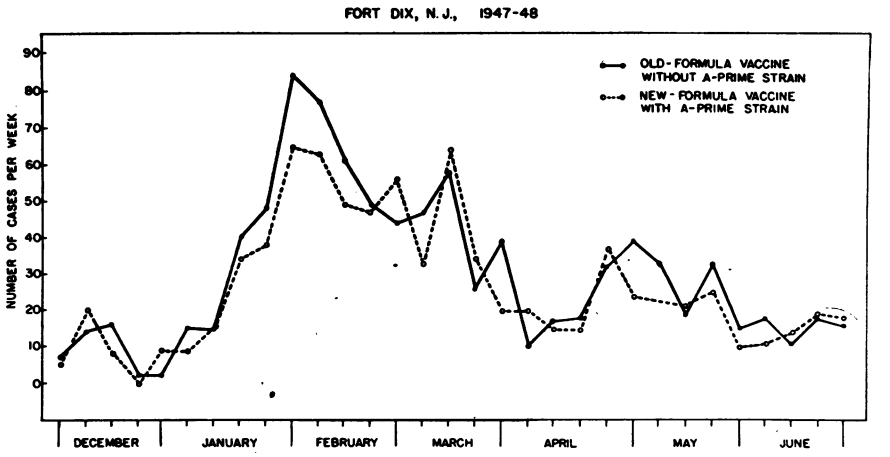
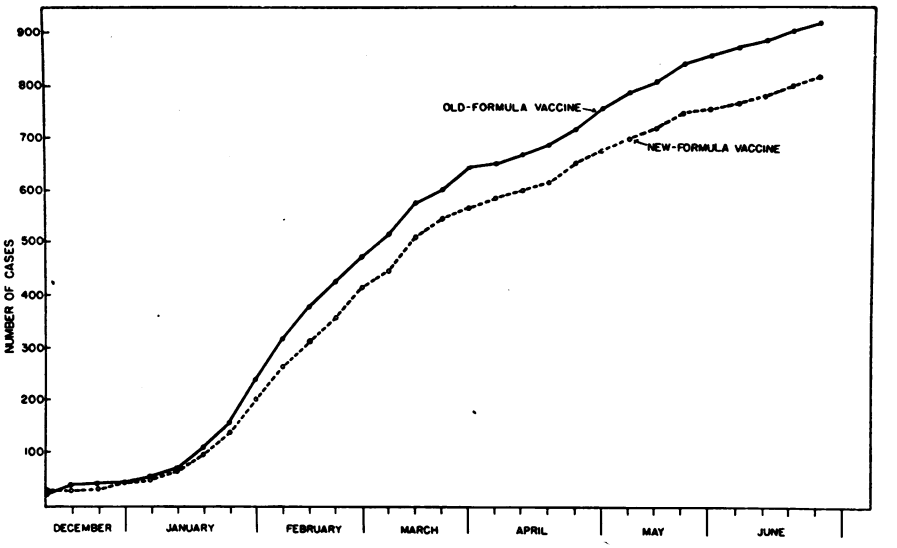


FIGURE 2

Comparison of Cumulative Number of Cases of Nasopharyngitis, Laryngitis and Bronchitis in Two Groups Given Old-formula and New-formula Influenza Virus Vaccine.

1 DEC., 1947 THROUGH 1 JULY, 1948



respiratory tract most prominently involved. It is for this reason that special attention was given to the group of cases diagnosed as nasopharyngitis, laryngitis, and bronchitis.

The data in Table 2 and Figure 1 indicate the number of patients hospitalized or put on quarters each week with such diagnoses. In almost all cases the presence of a temperature of 100° or higher was the basis for inclusion in these categories. It will be seen that in both odd and even serial-numbered groups, which had been given the "old"- and "new"-formula vaccines, respectively, there was a distinct increase in the incidence of respiratory disease beginning in mid-January and lasting until mid-March. Then, at the end of April and lasting a few weeks into May, there was a second noticeable increase.

It is difficult to see from Figure 1 that, during the period when the amount of respiratory disease was increased, the number of illnesses in the odd half of the population was somewhat in excess of that in the even half. This trend is shown more clearly when the data are presented cumulatively.

Figure 2 shows graphically (also see Table 2) the cumulative number of cases in the odd and even groups from December, 1947, to July, 1948. It is clear that the number of cases from the odd group exceeded the number of cases from the even group. The extent of the difference at the end of the observation period was 101 cases.

The question at once arises as to the significance of this difference. The data in the next few figures and tables are intended to help answer this question.

Figure 3 contains a graph of the cumulative number of admissions to hospital for a variety of conditions other than nasopharyngitis. The data for the months December, 1947, through April, 1948, include hospital admissions for injuries, surgery, venereal diseases, and neuropsychiatric conditions; and to these have been added admissions for tonsillitis, scarlet fever, pneumonia, otitis media, and mumps. The data for

the first group were kept only until the end of April, 1948, since the original intention was to conclude the study period as of the latter date. However, the graph was extended by charting the additional admissions for the infectious diseases mentioned, over the remainder of the period, because the nasopharyngitis group was carried to the end of June. The reason for the extension will be evident from the data in Figure 3.

Figure 3 shows that through the period of observation there was no difference in the cumulative admissions from the odd and even groups, in terms of the diagnoses noted above. In the majority of instances the respective points for any one week fall so close together as to be indistinguishable. The two inseparable lines describing the cumulative number of cases of "*other*" diseases are in contrast to the two distinctly divergent lines for *nasopharyngitis, etc.*, as shown in Figure 2.

Although the data in Figure 2 clearly indicate that a greater number of cases of respiratory disease had occurred in that half of the population with odd serial numbers, it is not easy to tell from the graph when this difference occurred or to what extent. In order to show this difference, a series of points was plotted (Figure 4) to demonstrate the extent to which the cumulative number of admissions from the odd group exceeded admissions from the even group at the end of each weekly period from December, 1947, to July, 1948.

Figure 4 shows a comparison of the curve expressing the degree of difference in the cumulative admissions from the odd and even groups for common respiratory disease (which would also include the influenzas) and for other diseases. It is readily seen that illnesses *other* than nasopharyngitis occurred in equal numbers of odd and even men throughout the observation period. This is indicated by the fluctuation of the difference curve near the zero-line.

Cases of common respiratory disease also occurred in equal numbers in odd and even groups during December, 1947, and early January, 1948. However, beginning in mid-January the number of cases among *odd* men began

FIGURE 3

Comparison of Cumulative Number of Cases of Illness other than Common Respiratory Disease in Two Groups Given Old-formula and New-formula Influenza Virus Vaccine

1 DEC., 1947 THROUGH 1 JULY, 1948

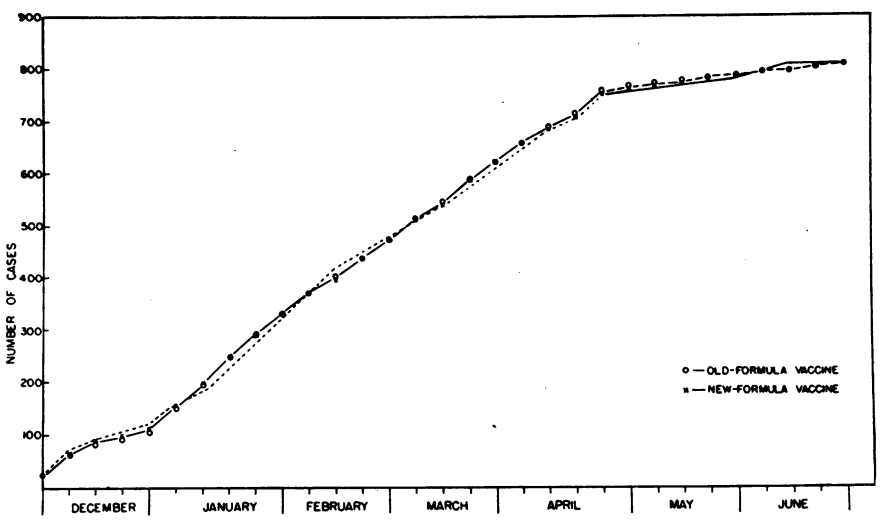
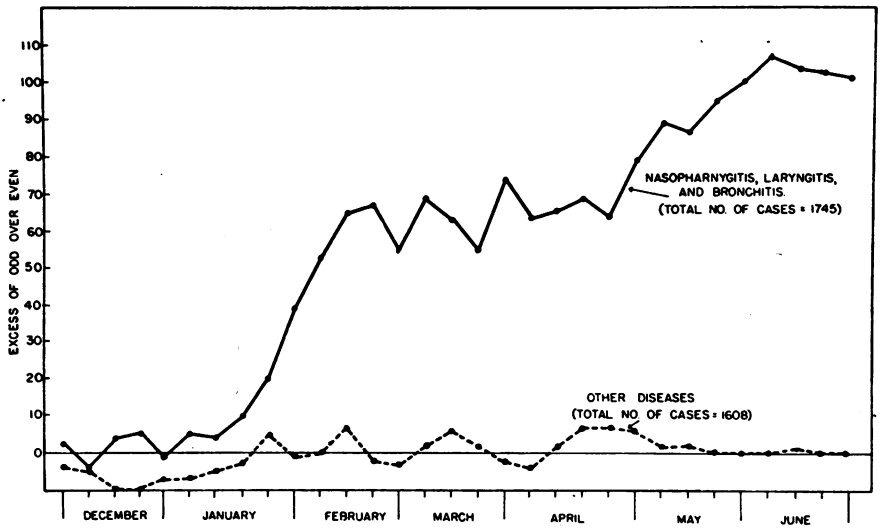


FIGURE 4

Difference in Cumulative Number of Cases of Illness in Odd- and Even-Numbered Men Given Old-formula and New-formula Influenza Virus Vaccine, Respectively



to exceed the number of cases from the *even* group. This continued until the end of February. Although, as shown in Figure 1, the high incidence of respiratory disease was maintained until the end of March, before declining to lower levels, the number of such cases among odd and even men was essentially the same through March and April. Then, during the second increase in common respiratory disease in April and May, there occurred another period when odd-numbered cases exceeded even-numbered ones. In June both groups were again equally represented.

It appears from these data that some factor was operative during the periods in January-February and April-May when the even-numbered group was favored with fewer cases of respiratory disease. It is to be recalled that the odd- and even-numbered groups differed with respect to one factor only; the even-numbered men had received the "new" vaccine containing antigens of the A-prime strain as well as the A and B strains, while the odd-numbered men had received so-called "old" vaccine that contained only the A and B antigens, but not the A-prime antigen.

It seems reasonable to conclude that the occurrence of 101 fewer cases of respiratory disease in that half of the population with even serial numbers was related to the treatment given. The data shown in the foregoing charts are summarized in Table 3.

For comparison with the numbers of odd and even men diagnosed as having had *nasopharyngitis, laryngitis,* and *bronchitis,* there is shown the number of cases of *other illnesses* from the odd and even groups. In addition the number of odd and even men in eight companies selected at random is tabulated for comparison. This number was selected to show how many odd and even men are found in a randomly selected group comparable in size to those in the illness categories.

It is clear that the difference of 101 cases of nasopharyngitis, etc., between the odd and even groups is significant in view of the fact that little or no difference between odd and even is evident in other categories of similar size. Al-

TABLE 3

Comparison of the Total Number of Cases of Common Respiratory Disease, and of Other Diseases, in Odd and Even Groups Occurring in the Interval December 1, 1947–July 2, 1948

	Number of Cases			Difference
	Total	Odd *	Even *	Odd-Even
Nasopharyngitis, etc.[1]	1,745	923	822	+101
Other Diseases [2]	1,608	804	804	0
Population Control [3]	1,691	848	843	+5

* The odd group received old-formula vaccine and the even group received new-formula vaccine.

[1] Includes cases hospitalized or put on quarters for illnesses diagnosed as nasopharyngitis, laryngitis, or bronchitis.

[2] Includes admissions to hospital for venereal disease, surgery, injuries, neuropsychiatric conditions as well as the pneumonias, tonsillitis, scarlet fever, otitis media, and mumps.

[3] Represents the number of men with odd and even serial numbers in eight companies selected at random.

TABLE 4

Tabulation of Number of Cases of Nasopharyngitis, etc., Among Men with Odd and Even Serial Numbers in 5 Successive Intervals Between December 1, 1947, and July 2, 1948

Inclusive Dates	Length in Weeks	Odd	Even	Excess of Odd over Even
Dec. 1–Jan. 15	6	56	51	+ 5
Jan. 16–Feb. 26	6	325	265	+ 60
Feb. 27–April 30	10	340	341	— 1
May 1–June 17	6	157	114	+ 43
June 18–July 2	3	45	51	— 6
Total	31	923	822	+101

though a statistical test for significance supports this statement, the data shown in Tables 4 and 5 are presented to strengthen the opinion that the divergence is probably due to a difference in the number of cases of influenza in the two groups and that this was brought about as a result of vaccination.

In Table 4 it is seen that the difference between odd and even, with respect to numbers of cases of nasopharyngitis, occurred in two distinct periods. From the serological data (to be presented below) it is evident that a flurry of influenza occurred during the first of these periods (January 16–February 26), and it may be presumed to have occurred in recognizable numbers during the second period (May 1–June 17).

Table 5 contains a comparison of the numbers of cases of nasopharyngitis in odd and even groups during the period of presumed virus activity and in the remainder of the observation period.

TABLE 5

Numbers of Cases of Nasopharyngitis, etc., from Odd and Even Groups in the Intervals of Presumed Influenza Virus Activity as Compared with the Remainder of the Observation Period

Periods of Presumed Virus Activity	Length in Weeks	Odd	Even	Excess of Odd over Even
Jan. 16–Feb. 26 May 1–June 17	12	482	379	+103
Remaining Periods				
Dec. 1–Jan. 15 Feb. 27–April 30 June 16–July 2	19	441	443	— 2
Total	31	923	822	+101

Although comparable numbers of cases occurred during both periods the difference between odd and even was evident only during the intervals January 16–February 26 and May 1–June 17.

SEROLOGICAL STUDIES

At the time the difference between the odd and even groups was recognized, serological tests had not yet been done on the acute and convalescent sera collected from patients hospitalized with respiratory disease. Paired specimens were collected from more than 500 individuals who were ill in the period of the highest incidence of illness. In view of the analysis shown in the foregoing, it was not surprising to find that a certain number of cases of influenza A had occurred; nor was it surprising that the strain of virus prevalent appeared to be, from the serological findings, more closely related to the 1947 virus (Type A-prime).

Of the group of 528 paired serum samples only 28, or about 5 per cent, were found to have significant antibody increases (4-fold or more) in the convalescent sera when tested with the FM1 strain (Type A-prime). Of the 28, only 4 were detected to have a 4-fold rise in titer when tested with the PR8 strain (Type A), and 9 more showed a 2-fold change in titer; thus suggesting a closer antigenic relationship to the A-prime subgroup of influenza virus Type A. It is interesting to note that 19 of the 28 positive cases were individuals with odd serial numbers, and 9 were from the even-numbered group.

The relatively small number of serologically positive cases indicates that only a small proportion of the illnesses responsible for the peak in February and March was due to the influenza virus. The cases examined serologically were those occurring in that period; blood for study was not obtained during the flurry in the late spring. The small number of cases of proven influenza were not concentrated in any particular organizations.

DISCUSSION

The serological data are of help in evaluating the clinical and epidemiological findings. The fact that the proportion of serologically proven cases of influenza was so low makes the difference of 100 cases between the odd and even groups more significant than if the proportion of influenza infections was high. It is not possible to estimate the per cent reduction in the influenza attack rate resulting from vaccination without resorting to too many assumptions in arriving at an estimate of the number of cases of illness attributable to the influenza virus. The result would be of questionable value. Suffice it to say that when two vaccinated groups of equal size in the same population were compared, the one given the vaccine that furnished the broader antigenic coverage experienced approximately 100 fewer cases of respiratory disease as compared to a similar group given a vaccine that was defective with respect to the particular antigen for the prevalent virus.

Largely because of the nature of the "control" group and the low incidence of cases of proven influenza, it is not desired to draw far-reaching conclusions from this study. Nevertheless, several things have been learned.

1. As an addition to information from earlier studies, which indicated that vaccination reduces susceptibility to naturally occurring influenza A and B, the present investigations show that susceptibility to the disease caused by a virus of the A-prime sub-group can also be reduced by vaccination. The failure of vaccination to influence susceptibility in the spring of 1947, together with the findings in the present study, emphasize the necessity for continuing to include the new antigen in

vaccines of the future, and emphasize a problem long recognized, namely the necessity for further study to determine the most effective antigenic formula.

2. From independent studies of the Fort Dix epidemiological data by Dr. Philip Sartwell, of the School of Hygiene of Johns Hopkins University, as well as the observations that have been described, it seems that influenza *did not* occur in epidemic proportions at Fort Dix during the period of this study. Accordingly, it might be concluded that a proportion, at least, of influenza virus infections that occur *sporadically* or *endemically* can be prevented by vaccination.

Even though influenza vaccines may not yet be complete in their coverage they do contain, nevertheless, antigenic components for certain viruses that are potentially the cause of moderately severe disease in man that may be extensively disseminated, sporadically or epidemically.

In closing, a word of optimism is in order to counteract opinions that have emanated from various quarters of disappointment in the "failure" of vaccination to influence susceptibility to influenza in the spring of 1947. In the opinion of others, the so-called failure has been regarded as a finding of great importance. One cannot escape the fact that at that time an etiologic agent was discovered capable of causing widespread disease in man, and by virtue of the vaccination studies, its antigenic difference from previously isolated strains of influenza virus Type A was clearly recognized. Some have stated that this strain is a "mutation" and that this might mean that we will always be immunizing against a disease that occurred the year before.

There seems to be something wrong with this idea from a biological viewpoint. It might be questioned whether the new strain may not have prevailed at some previous time. It is entirely possible that it may have escaped detection in recent years, or that it had been more active prior to the time when the influenza viruses were so easily isolated.

It is a more hopeful view to consider that there is a finite number of antigenic varieties, or sub-groups, and that we may not yet have them all in the various laboratories throughout the world, nor is the classification yet complete.

The results of the work of the strain study center of the Influenza Commission and the results of the field studies, already under way for 1948–1949 and to be continued indefinitely into the future, should provide the answers.

SUMMARY

1. In the winter of 1947–1948 studies on vaccination against influenza were carried out in a military installation. Due to limiting circumstances that are described, the study involved a comparison of two vaccines that differed in strain composition. Representative strains of Type A and Type B viruses were present in both. However, only one of the two vaccines contained, in addition, the antigenic variant of the Type A strain (referred to as A-prime) that was prevalent during the winter and spring of 1946–1947.

2. The entire population was vaccinated; men with odd serial numbers received one of the vaccines and the even-numbered men received the other. Records were kept of admissions to hospitals and to quarters for all diseases. The data revealed that the group given the new-formula vaccine, which contained the A-prime antigen, experienced approximately 100 fewer cases of respiratory disease. As for other illnesses there was no difference, in this respect, between groups given the different vaccines.

3. Serological tests of acute and convalescent sera revealed the occurrence of a small proportion of cases of influenza virus infections during the period of increased prevalence of respiratory disease. Moreover, from the serological studies it appears that the prevalent virus was related to the A-prime sub-group, which was represented in only one of the two vaccines.

4. These observations indicate that during a period in which *influenza occurred sporadically or endemically,* the use of a vaccine hav-

ing the specific as well as the broader antigenic coverage, was effective in reducing the number of cases of respiratory disease.

5. The significance of the existence of antigenic varieties of influenza virus strains is discussed in relation to the problem of immunization.

ACKNOWLEDGMENTS: These studies could not have been undertaken without the interest and willing coöperation of certain key persons in the organizations involved. It is a pleasure to express our grateful appreciation to Lt. Col. Frank W. Threadgill, Post Surgeon at Fort Dix; to Col. Charles W. Farinacci, Commanding Officer of the First Army Area Medical Laboratory; and to Col. Leroy D. Soper, Commanding Officer of Tilton General Hospital. It is desired to acknowledge, too, the generous assistance of the staffs of the respective organizations.

As noted in the text, these studies were initiated following the advice of a committee of the Army Epidemiological Board and of members of the Office of the Surgeon General. The advice and suggestions of the committee in planning the work are greatly appreciated. It is desired to acknowledge particularly the helpfulness of Col. Tom F. Whayne, Lt. Col. Frank L. Bauer, and Maj. Thomas G. Faison. The continued interest and advice of Dr. Thomas Francis, Jr., is warmly appreciated.

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Mental Hygiene Statistics

The Division of Mental Hygiene of the U. S. Public Health Service on November 1, 1948, published the first of a series of current reports on Mental Hygiene Statistics to be designated as the MH-S series, and making available the results of the annual Survey of Patients in Mental Institutions earlier than the final published report. The first report shows by states and regional division normal capacity, percentage of overcrowding, the full-time administrative staffs, and expenditures for the maintenance of state hospitals for mental disease in 1946. The Annual Census of Patients in Mental Institutions was transferred from the Census Bureau to the Public Health Service early in 1948.